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5.20 Leukaemias

Understanding pathogenesis through similarities and differences

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SUMMARY

- Globally, there is a lack of population-based descriptive data for many leukaemia subtypes, of which there are more than 30. This information is required to inform etiological hypotheses, plan health-care services, and monitor the impact of therapeutic change.
- Different subtypes of leukaemia dominate at different ages. For example, B-cell acute lymphoblastic leukaemia is most common in children younger than 15 years, and chronic lymphocytic leukaemia, myeloproliferative neoplasms, and acute myeloid leukaemia are far more common at older ages.
- For reasons that are unknown, almost every leukaemia subtype has a male predominance.
- In high-income countries, survival rates vary widely from one subtype to another. The 5-year relative survival is more than 80% for chronic lymphocytic leukaemia and chronic myeloid leukaemia but less than 20% for other subtypes, such as acute myeloid leukaemia.
- Increased understanding of pathogenesis has resulted in marked improvements in survival for some leukaemia subtypes, including chronic myeloid leukaemia.

The leukaemias (literally “white blood”) comprise a heterogeneous group of more than 30 lymphoid and myeloid malignancies with diverse etiologies, treatment pathways, and outcomes [1]. They are classified by cell of origin (Fig. 5.20.1).

Leukaemias were first recognized as a distinct entity in the 1850s [2]. The taxonomy of leukaemias has changed markedly over time, as biological understanding of the similarities and differences between the various haematological malignancies – leukaemias, lymphomas, and myelomas – and their relationship to the normal bone marrow and immune system has increased. However, contemporary population-based information about the occurrence and outcome for many leukaemia subtypes is sparse, and for some of the rarer entities is mostly non-existent.

This absence of data largely reflects the paradigm-changing nature of the WHO classification implemented in 2001 (the basis for the International Classification of Diseases for Oncology, third edition [ICD-O-3]), which, for the first time, incorporated genetic data with information on immunology, morphology, and clinical parameters [3]. This resulted not only in significant refinements to previously defined categories but also in the addition of several new entities, including the myelodysplastic syndromes and myeloproliferative neoplasms, which form part of the myeloid leukaemia spectrum.

Critically, most of the neoplasms listed in the ICD-O-3 categories of myelodysplastic syndromes and myeloproliferative neoplasms still appear with a code beginning with “D” (neoplasms of unknown or uncertain behaviour) in the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).

Such radical changes in classification, together with the breadth of investigations required to implement the classification system (histology, cytology, immunophenotyping, cytogenetics, flow cytometry, and clinical data), continue to pose significant challenges for population-based cancer registries; many struggle to capture all diagnoses, and often continue to report using the traditional leukaemia grouping [4,5].

In 2018, there were an estimated 437 000 new cases of leukaemia worldwide, and leukaemia was the 15th most common cancer type, accounting for 2.4% of all new cancer cases [6]. However, because many countries still do not have high-quality and representative cancer registration systems, examining global variation and trends over time is challenging for any cancer type; for leukaemias, the situation is exacerbated by the diagnostic challenges associated with identifying the various leukaemia subtypes, coupled with the inconsistent implementation of the WHO classification [1,7,8]. Furthermore, even in countries with good cancer registration systems,

there is a lack of consistency in the policies applied to progressions and transformations (e.g. from myeloid dysplastic syndromes to acute myeloid leukaemia [AML]); for example, the United States Surveillance, Epidemiology, and End Results (SEER) programme has different rules to the European Network of Cancer Registries [9,10].

In low-income countries, where mortality and morbidity from infections and nutritional conditions are often high, diagnosing leukaemia presents additional challenges. The symptoms of many types of leukaemia are broadly similar to those of infectious and/or parasitic illnesses, and the diagnostic expertise and/or technologies required to enable leukaemia to be distinguished from background infections are often lacking.

Descriptive epidemiology

Good-quality population-based descriptive data are required not only to inform etiological hypotheses and plan health-care services but also to monitor the impact of therapeutic change in the general population. This need is particularly pertinent in fast-moving areas like haemato-oncology, where treatment protocols are subject to rapid change, and “gold standard” randomized controlled trials, which tend to be conducted almost exclusively in higher-income countries, are frequently restricted to specific patient subgroups, often comprising younger people with fewer comorbidities. Furthermore, in some countries, particularly low-income countries and/or those where universal health coverage is lacking, the likelihood of both treatment and trial entry often varies with socioeconomic status, sex, and ethnicity.

In recent years, there has been an increasing recognition that scientific progress is being impeded by the lack of reliable population-based incidence and survival data on the various leukaemia subtypes [11]. This has led to improvements in national cancer registration procedures

as well as the development of several specialist registries [12,13]. One such source is the United Kingdom Haematological Malignancy Research Network (HMRN; <https://www.hmrn.org>), which since 2004 has collated detailed information on all newly diagnosed haematological malignancies arising in a population of about 4 million [14]. The HMRN data for the 12 years from September 2004 to August 2016 ($n = 29\,329$) for the major subtypes (Fig. 5.20.2) illustrate where the leukaemias sit within the broad WHO ICD-O-3 cell-of-origin haematological malignancy spectrum.

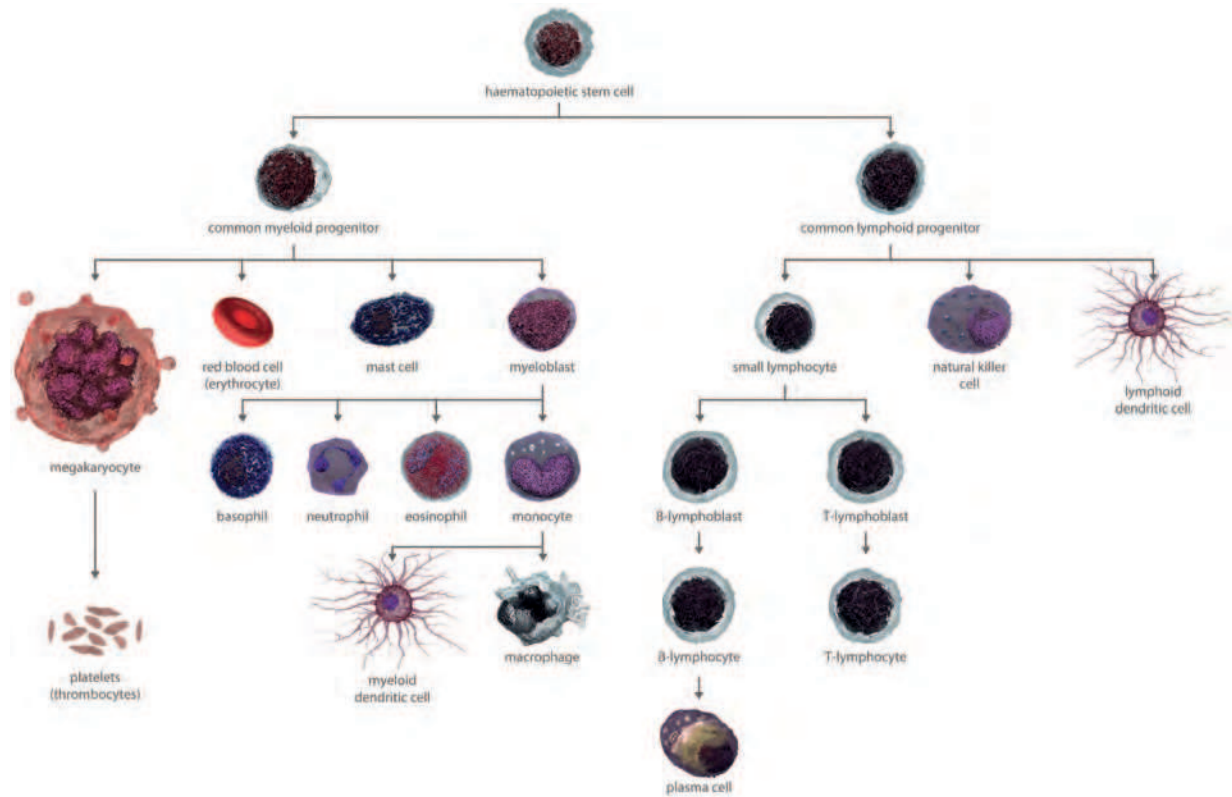
The leukaemias account for about 40% of all haematological malignancies. They comprise all myeloid subtypes and several lymphoid subtypes. The main leukaemia subtypes are shown in Fig. 5.20.3. Mature B-cell chronic lymphocytic leukaemia (CLL) is the largest category, followed by the myeloproliferative neoplasms, the AMLs, and the myelodysplastic syndromes.

Historically, when CLL cells were found in lymph nodes rather than in peripheral blood, the disease was termed small lymphocytic lymphoma. The different names reflected differences in disease spread rather than in origin. For research purposes, CLL is increasingly grouped with other mature B-cell malignancies, both lymphomas and myelomas, and/or with the non-Hodgkin lymphomas, both T-cell and B-cell; the same is true for hairy cell leukaemia, which also has a mature B-cell origin [15,16]. However, most population-based registries still include CLL and hairy cell leukaemia in their “all leukaemia” category [4,11].

For information and completeness, data on monoclonal B-cell lymphocytosis, which has an ICD-O-3 behaviour code of 1 (and is not listed in ICD-10), are also included in Fig. 5.20.3. Monoclonal B-cell lymphocytosis is defined by a monoclonal B-cell count of less than $5 \times 10^9/L$ in peripheral blood [1]. Because about 75% of cases have a CLL phenotype, monoclonal

FUNDAMENTALS

- Originating in blood-forming tissues, usually the bone marrow, the leukaemias comprise a heterogeneous group of lymphoid and myeloid malignancies. This simple topographic categorization – cancer in the blood – reflects the pattern of spread rather than the origin.
- The 2001 WHO classification of haematological malignancies, which groups cancers according to their cell of origin, was adopted into worldwide clinical practice but did not have an immediate effect on population-based epidemiological research. Increasing recognition that the lack of data on clinically meaningful groups was impeding scientific progress has led to recent improvements in national cancer registration procedures as well as the development of specialist registries.
- Although the majority of leukaemia subtypes do not appear to have major environmental determinants, a few well-established risk factors continue to produce strong associations, for example cytotoxic chemotherapy and/or radiotherapy and acute myeloid leukaemia/myelodysplastic syndromes.
- Knowledge relating to genetic determinants has increased markedly over the past 5 years. The number of predisposition syndromes recognized to be associated with certain leukaemia subtypes is increasing, and a chapter on myeloid neoplasms with germline predisposition is included in the most recent WHO classification.
- The leukaemias have led the field of cancer genomics. Since the advent of the first targeted cancer therapy (tyrosine kinase inhibitors), advances in molecular biology and therapy have continued to transform the landscape for several – but by no means all – leukaemia subtypes.

Fig. 5.20.1. Overview of haematopoiesis. Leukaemias are classified by cell of origin.

B-cell lymphocytosis is increasingly being studied with a view to increasing the understanding of pathogenesis of CLL (defined by a monoclonal B-cell count of $\geq 5 \times 10^9/\text{L}$ with CLL morphology and phenotype).

The overall incidence of leukaemia, like that of many other types of cancer, increases with increasing age, and the incidence rate is higher in men than in women. However, in contrast to many other cancer types, leukaemias can occur at any age, and different subtypes dominate at different ages. The heterogeneity of the various leukaemia subtypes (excluding monoclonal B-cell lymphocytosis) is illustrated in Fig. 5.20.4, which distributes the data by age at diagnosis and sex.

Acute lymphoblastic leukaemias (ALL), notably B-cell ALL, which accounts for less than 4% of the total, predominate in children younger than 15 years, an age group in which some leukaemia subtypes are often rare or non-existent. In

contrast, at older ages, CLL, the myeloproliferative neoplasms, and the AMLs are far more common (Fig. 5.20.4). Variations with sex are also marked; the overall male predominance is evident across the full age spectrum and the main diagnostic subtypes.

Additional differences are evident within subtypes [17], as illustrated in Fig. 5.20.5, which presents sex rate ratios for myelodysplastic syndromes and AML. Myelodysplastic syndrome with deletion of chromosome 5q has a strong female predominance, in contrast to the other subtypes of myelodysplastic syndrome. AML with myelodysplasia-related changes has a strong male predominance, whereas AML with *MLL* rearrangement is more common in females.

Risk factors

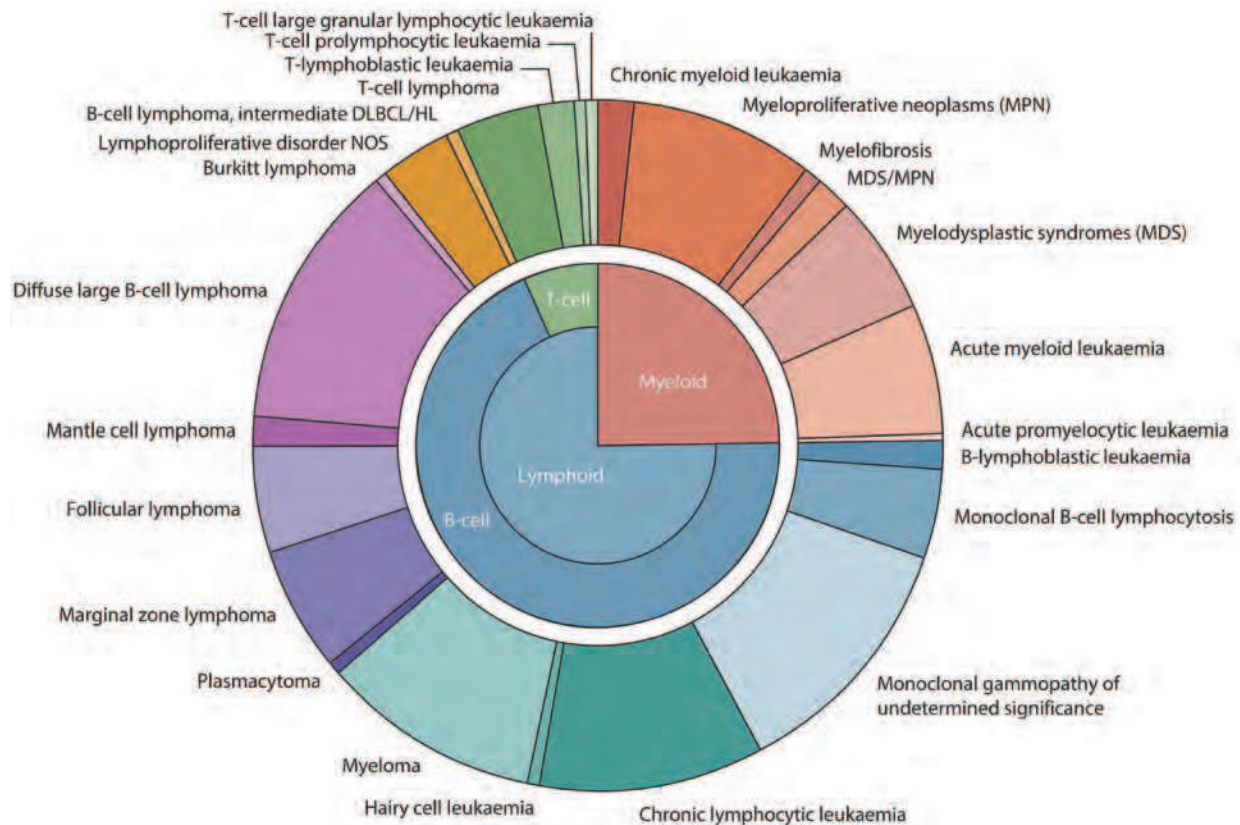
Like all diseases, the leukaemias have both genetic and environmental determinants to their etiology,

and the relative contribution of each varies from one subtype to another.

With respect to environmental exposures, relatively little has changed in the past 5 years; well-established risk factors continue to produce strong associations but explain only a small proportion of the total burden of disease. Examples of such associations include those with cytotoxic chemotherapy, benzene, ionizing radiation, and viral infections such as human T-cell lymphotropic virus type 1 (HTLV-1), which is a necessary but not sufficient cause of the comparatively rare adult T-cell leukaemia/lymphoma (see Chapter 2.2). HTLV-1 causes leukaemia in about 5% of people infected with the virus. Although HTLV-1 is endemic in parts of Japan, South America, Papua New Guinea, Africa, and the Middle East, it is hardly ever found elsewhere.

With respect to broader environmental associations, systematic trends with frequently used proxies of exposure are rarely observed

Fig. 5.20.2. Diagnostic distribution of haematological malignancies classified by the International Classification of Diseases for Oncology, third edition (ICD-O-3). Data from the Haematological Malignancy Research Network (HMRN) for 2004–2016 ($n = 29\,329$). DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; NOS, not otherwise specified.



for leukaemias, in contrast to many other cancer types. For example, in high-income countries the incidence of several common cancer types tends to vary with regularly used markers of socioeconomic status or lifestyle, including education level, income, and deprivation level, for reasons that are related either to etiology – exemplified by lung cancer and smoking, or cervical cancer and human papillomavirus (HPV) infection – or to detection, as illustrated by colon cancer and screening. The consistency of such observations often helps to target public health interventions and policies that aim either to prevent the development of disease (see Chapter 6.1) or to detect it at an early stage (see Chapter 6.6).

However, for the leukaemias, coherent patterns of this type are rarely observed. Findings from epidemiological studies examining the

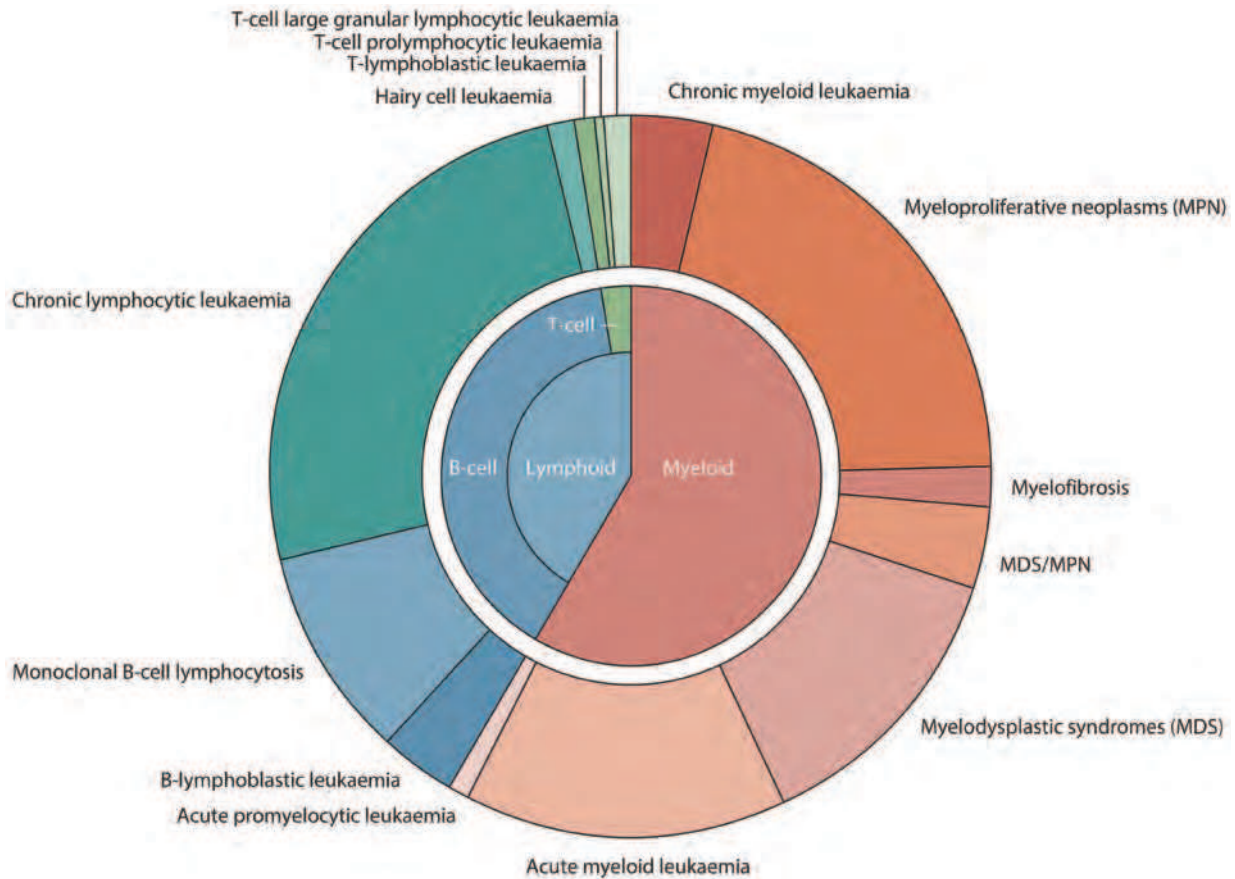
potential etiological role of specific risk factors, such as exposure to antibiotics, non-ionizing radiation, or hair dyes, often produce results that are weak and inconsistent. An extensive up-to-date review of all the evidence relating to the environmental determinants of leukaemia in children and adults can be found in the latest edition of *Cancer Epidemiology and Prevention* [18].

As with environmental determinants, certain genetic features that predispose towards leukaemia have long been known. Perhaps the most notable is male sex, which is generally associated with an increased risk across the age spectrum (Fig. 5.20.4). In addition, certain congenital disorders are strongly associated with the subsequent development of the acute leukaemias, usually those occurring in children, adolescents, or young adults. Examples are the associa-

tion of Down syndrome with AML and ALL and of Fanconi anaemia and other bone marrow failure syndromes with myelodysplastic syndromes and AML.

In contrast to knowledge about environmental determinants, knowledge relating to the genetic determinants of several leukaemia subtypes has increased markedly over the past 5 years. This increase is, at least in part, due to the advent of new genomic technologies and their growing accessibility to the wider scientific community. As a result, the number of predisposition syndromes recognized to be associated with certain leukaemia subtypes, particularly (but not exclusively) those of the myeloid lineage, has increased considerably. Knowledge in this area is advancing rapidly. A chapter on myeloid neoplasms with germline predisposition (inherited and de novo) is, for the first time, included in the

Fig. 5.20.3. Diagnostic distribution of leukaemias (including monoclonal B-cell lymphocytosis) classified by the International Classification of Diseases for Oncology, third edition (ICD-O-3). Data from the Haematological Malignancy Research Network (HMRN) for 2004–2016 ($n = 11\,231$).



most recent WHO classification, and associations between genetic conditions and lymphoid leukaemias, notably B-cell ALL, are also discussed in the relevant chapters [1].

Genomics, survival, and treatment

The leukaemias have led the field of cancer genomics. In the 1960s, the Philadelphia translocation was discovered in chronic myeloid leukaemia (CML), a subtype of myeloproliferative neoplasms. This discovery eventually resulted in the development of the first targeted therapy in cancer, a BCR-ABL tyrosine kinase inhibitor, which has transformed outcomes in CML [19].

Chromosomal analysis, undertaken through either classical or molecular techniques, has been

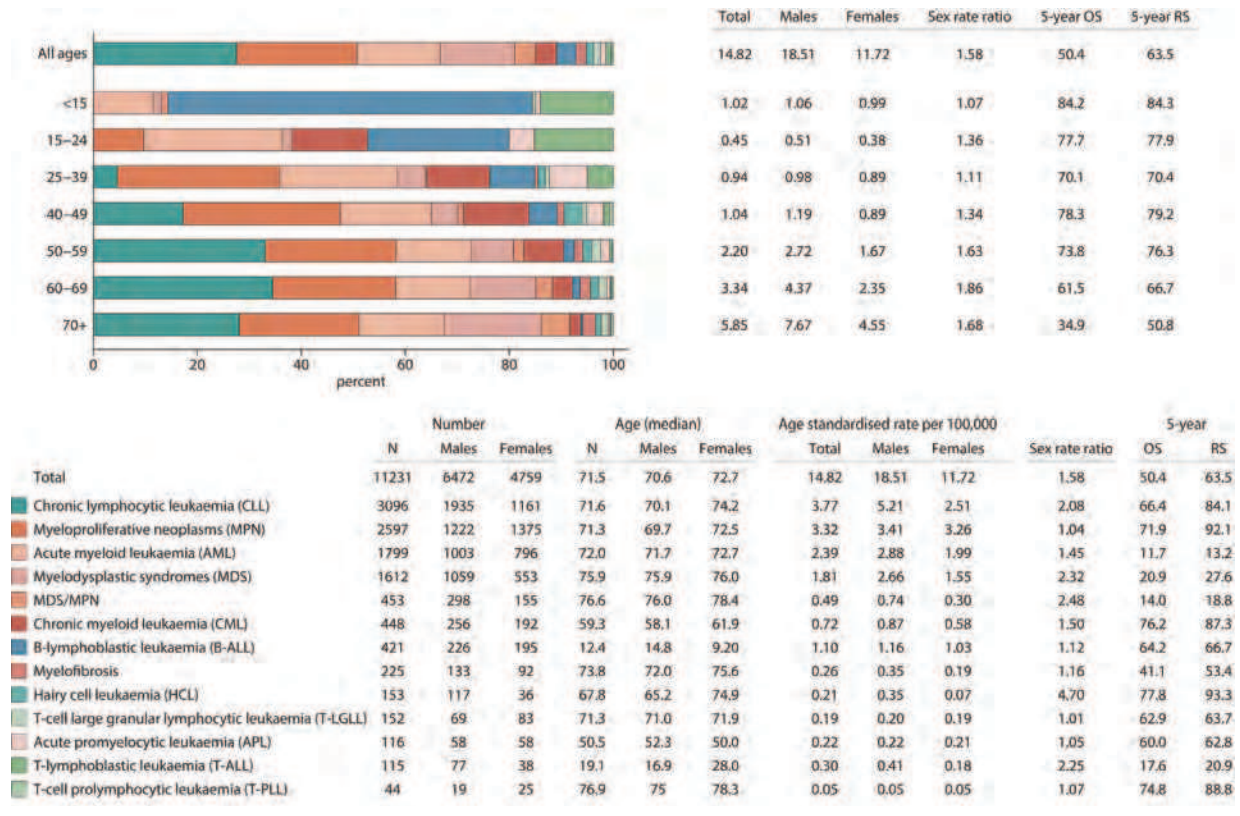
part of routine clinical practice for many decades [1]. However, these methods have limitations. Conventional cytogenetics are limited to detecting structural changes at a chromosome level, whereas smaller abnormalities such as point mutations are not detectable, and molecular cytogenetics can only be targeted at known abnormalities.

Accordingly, new techniques that have been developed in the past 15 years are increasingly being used for the diagnosis, classification, and prognostication of the leukaemias. These include DNA sequencing and array-based platforms with next-generation sequencing, which currently provides the greatest genomic resolution (see Chapter 3.2). Recent studies using these techniques are revealing the complexity of many leukaemia subtypes [20–23], many

of which – unlike the single chromosomal translocation and resulting aberrant fusion protein in CML – have complex pathogenic pathways. Although next-generation sequencing and other techniques are rapidly becoming part of routine diagnostic practice in some settings, the incorporation of this information in other settings, particularly in low-income countries, remains challenging.

The scientific advances that have led to improvements in survival for some leukaemia subtypes are a major success story. In high-income countries, survival rates for paediatric B-cell ALL now exceed 90%, and survival rates for acute promyelocytic leukaemia, a subtype of AML, are about 80%. Tyrosine kinase inhibitors have transformed CML from a comparatively rare fatal cancer to a long-term condition

Fig. 5.20.4. Incidence proportions of leukaemias (excluding monoclonal B-cell lymphocytosis) distributed by subtype within age strata, age-standardized (world, 2000–2025) rates per 100 000, and 5-year overall survival (OS) and relative survival (RS). Sex rate ratio is male rate divided by female rate. Data from the Haematological Malignancy Research Network (HMRN) for 2004–2016, followed up September 2018.



with a survival rate that approaches that of the general population. Such progress has redirected the research efforts to other types of leukaemia, and to other cancer types.

However, despite these improvements, the outlook for older people and those with aggressive subtypes remains poor. Contemporary estimates of 5-year overall survival and relative survival from the HMRN population-based patient cohort are shown in Fig. 5.20.4, both by age strata for all subtypes combined and by major subtype by all ages combined. The corresponding relative survival curves are shown in Fig. 5.20.6.

Although some subtypes of AML are potentially curable with intensive chemotherapy, over the past three decades there has been little improvement for the majority of AML patients. The 5-year relative survival for AML in the HMRN

population-based data is 13.2%. For AML, the median age at diagnosis is about 70 years. Although the frequency of curative therapy is relatively high in younger patients, who often comprise the focus of clinical trials involving ALLs as well as AMLs, the inability of some patients, notably older patients, to tolerate intensive chemotherapy regimens remains problematic.

The increased application of genomic technologies is leading to the development of new targeted agents, including monoclonal antibodies. However, at present, most of these agents still need to be used in conjunction with intensive chemotherapy, so little progress has been made to date for the treatment of patients who cannot tolerate such regimens [24].

In contrast, the outlook for patients with more indolent leukaemias, including CLL (5-year relative

survival, 84.1%) and the myeloproliferative neoplasms (5-year relative survival, 92.1%), is relatively good, despite the fact that these cancers are currently incurable. The pathways of patients with these more chronic cancers often follow a remitting–relapsing course, with patients being monitored until chemotherapy treatment is required, and some never receiving treatment at all.

Prevention and early detection

In recent decades, advances in molecular biology and therapy have transformed the landscape for several leukaemia subtypes. However, in general this progress has not been matched by similar insights into the etiological determinants of the majority of leukaemias. In such circumstances, the development of preventive strategies that will affect the total burden of leukaemia

is challenging. However, it is clear that reduction in population exposures to well-known leukaemogenic agents such as polycyclic aromatic hydrocarbons should be pursued. In addition, radiological diagnostic and therapeutic procedures involving ionizing radiation should be used only when clinically required, and at the lowest possible doses.

With respect to the potential impact on high-risk groups, more careful monitoring of individuals with recognized leukaemia predisposition syndromes or other genetic susceptibilities is one area where improvements could be made. For example, the onset of bone marrow failure, a prelude to AML, could perhaps be detected at an earlier stage, enabling pre-emptive haematopoietic stem cell transplantation to be undertaken.

However, in situations where primary prevention is not possible, early detection and improved treatments tend to be the major focus. In this respect, the landscape for the leukaemias is changing rapidly, with new diagnostic technologies and less toxic targeted novel agents emerging, providing considerable promise for the future.

Fig. 5.20.5. Sex rate ratios (male rate divided by female rate) for subtypes of myelodysplastic syndromes and acute myeloid leukaemia (AML).

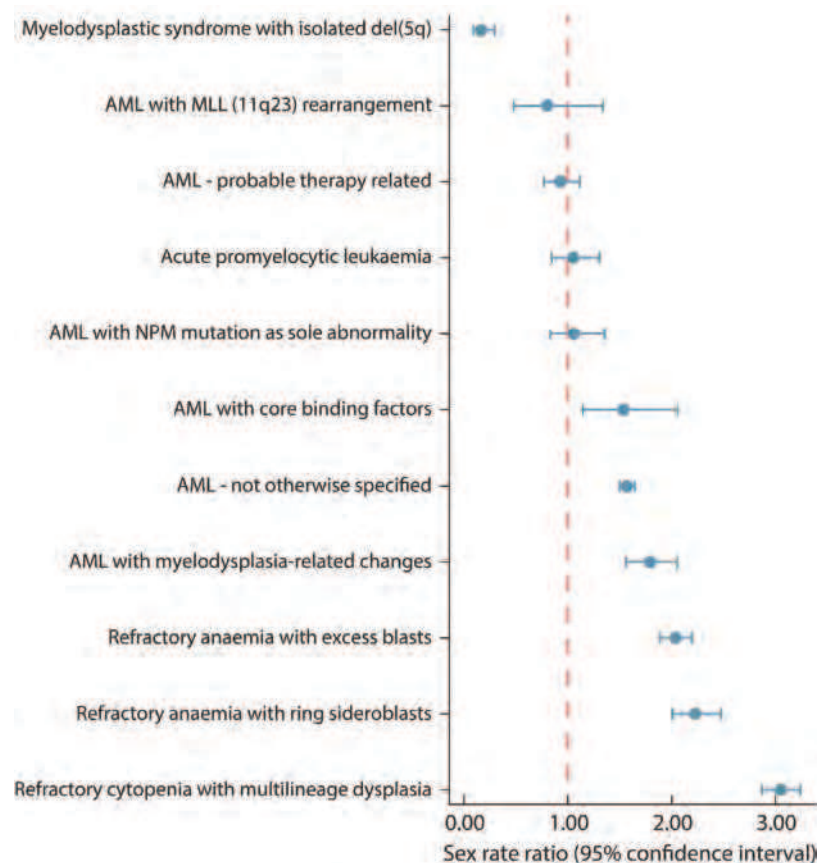
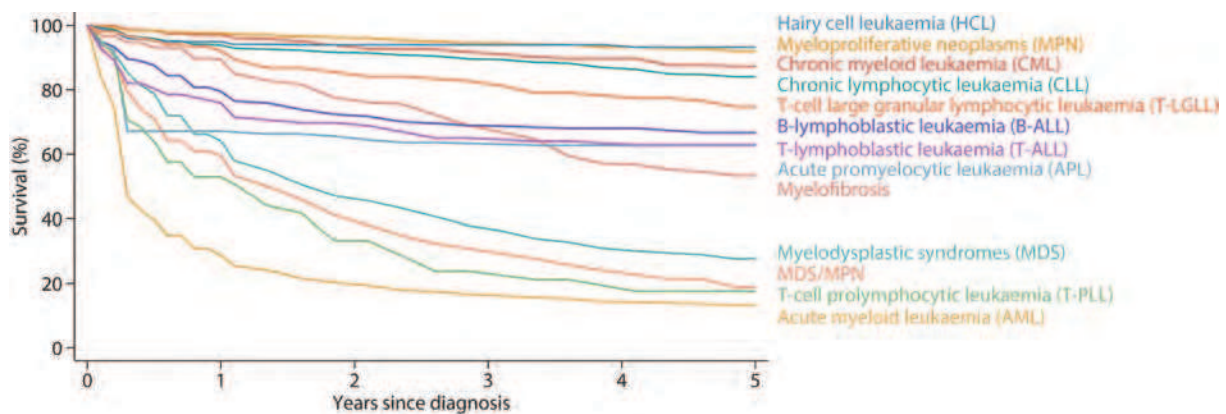


Fig. 5.20.6. Relative survival curves for leukaemias classified by the International Classification of Diseases for Oncology, third edition (ICD-O-3). Data from the Haematological Malignancy Research Network (HMRN) for 2004–2016, followed up September 2018.



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